The interview conducted on March 23, 2005, between Examiner Cook and applicant's undersigned attorney is hereby gratefully acknowledged. In this interview, a proposed response to the official action of November 23, 2004, was discussed, which response was eventually filed on March 23, 2005, along with a Request for Continued Examination, which included a request under 37 C.F.R. §1.03(c) for a three-month suspension. In the interview, the examiner stated that, if applicant could show support for the species that were being excluded by the proviso, she would withdraw the rejection. Accordingly, as rhinovirus is recited on page 10, line 25, in a list of conditions that the instant mention is useful to treat, the examiner agreed to withdraw the new matter rejection of claim 52. The examiner further agreed that if claim 37 were amended to recite "through the mouth" and if the response pointed out where there was implicit support for this recitation, then the rejection of claim 37 would be withdrawn. All of these issues were discussed and dealt with in applicant's amendment of March 23, 2005.

With respect to the rejection of claim 37 over Eby, applicant suggested deleting the word "about" so as to solve the problem mentioned in the official action. The examiner agreed that such an amendment should resolve the issue raised in the official action. This was done in the amendment of March 23, 2005.

The rejection over the Amgen reference was also discussed and applicant's attorney explained that Amgen did not explicitly disclose oromucosal administration but only

generally referred to oral or nasal administration. It was pointed out that one of ordinary skill in the art would understand that the term "oral" as used in Amgen means swallowing and "nasal" means administering directly to the lungs. The examiner stated that such arguments would need to be supported by a declaration submitted by an expert in the art, supported by literature references.

Claims 22-57 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Amgen in view Iida. The examiner states that Amgen discloses a method of treating viral infections using greater than about 20×10^6 IU of interferon. The examiner concedes that the present claims differ over Amgen in reciting "oromucosal contact." However, the examiner states that Amgen discloses that the interferon can be administered nasally, and it is well known that a product administered intranasally will contact the oromucosa. Further, the examiner states that the specification indicates that nasal administration is contemplated in the instant application. The examiner notes that applicant has argued that nasal administration usually means administration directly into the lungs to make direct contact with the virus there and does not mean administering in such as way as to remain in the nasal pharyngeal cavity. The examiner states that this argument is not persuasive, however, since it is not claimed and, furthermore, Iida discloses that intranasal administration of IL is delivered to the lungs where it activates an immune response. This rejection is respectfully traversed.

Those of ordinary skill in the art would understand that Amgen's reference to nasal administration would not be considered to encompass oromucosal administration. Nasal administration would be understood to mean administration directly into the lungs so as to be transferred to the bloodstream, or otherwise to act, through the lungs. At the time of the present invention there would have been no understanding that this language encompassed oromucosal administration. At the interview, the examiner stated that such arguments should be supported by a declaration of an appropriate expert. Accordingly, attached hereto is a declaration of Dr. Tovey, dated May 24, 2005, explaining why one of ordinary skill in the art reading Amgen would not consider the disclosure as suggesting that the interferon could be administered by oromucosal contact, which does not involve entry of the interferon into the bloodstream. This declaration is supported by many relevant publications.

As stated in the Tovey declaration, reference to "nasal routes" in Amgen can be considered to be delivery to the lungs. The examiner appears to agree with this when pointing out that Iida discloses intranasal delivery and explicitly states that the administration site is the lungs. See page 232, first column, half-way down, where it states:

> These results suggest that i.n. administration of these cytokines is likely to cause an inflammatory response, or that it activates the immune system at the administration site (lungs) and consequently stimulates host resistance against the viral infection. [emphasis added]

Whether the administration to the lungs causes transfer to the bloodstream or activation of phagocytes or direct action against a viral infection in the lung is not material to the discussion of Amgen. The issue is whether the term "administration by the nasal route" comprehends oromucosal administration. Iida would suggest that it does not. Administration by the nasal route would be interpreted by one of ordinary skill in the art as requiring administration to the lungs. The Tovey declaration makes clear that the state of the art at the time of Amgen was such that administration by the nasal route was intended to mean administration to the lungs.

The examiner states that the present claims do not exclude administration directly into the lungs. However, this statement is not accurate. The claims state that the interferon is administered "via oromucosal contact." This term is defined in the present specification. See, for example, page 17, lines 16-22, where it states:

> For the purposes of the animal experiments described in this specification, it will be clearly understood that the expressions "oromucosal" or "oropharyngeal" or "intranasal/oral" or "intranasal plus oral" or "i.n./o.r." with reference to the route of administration of IFN is to be taken to mean administration of the IFN preparation deep into the nasal cavity so that it is rapidly distributed into the oromucosal cavity, i.e. the mouth and throat of the recipient mammal, so as to make contact with the mucosa lining this cavity.

Furthermore, the examiner's attention is invited to page 12, lines 11-19, which include specific discussion of the intranasal route. This paragraph reads:

> The IFN may be administered by any means that provides contact of the IFN with the oromucosal cavity of the recipient. Thus it will be clearly understood that the invention is not limited to any particular type of formulation. The present specification describes administration of IFN deep into the oromucosal cavity; this may be achieved with liquids, solids, or aerosols, as well as nasal drops or sprays. Thus the invention includes, but is not limited to, liquid, spray, syrup, lozenges, buccal tables, and nebuliser formulations. A person skilled in the art will recognize that for aerosol or nebuliser formulations the particle size of the preparation may be important, and will be aware of suitable methods by which particle size may be modified. [emphasis added]

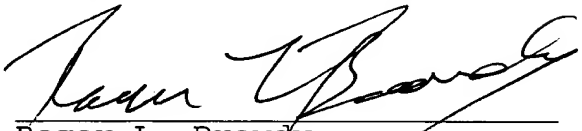
Those of ordinary skill in the art will understand that this reference to particle size in aerosol or nebulizer formulations means that the particle size is selected so that the particles will be deposited in the oromucosal cavity, rather than travel all of the way to the lungs. It is well known that fine aerosols are inhaled into the lungs, while aerosols with large particle size are deposited in the nasal pharyngeal cavity, which is part of the oromucosa. Accordingly, the definition of "via oromucosal route," as this term is used in the claims, must be taken from the specification and understood to mean in a manner that the medicament is deposited in the oromucosal cavity and not merely bypassing the oromucosal cavity on the way to the lungs, which is the intended administration site.

Accordingly, in light of the attached declaration of Dr. Tovey and the articles cited therein, as well as the arguments presented herein, reconsideration and withdrawal of this rejection is respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By 
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

		Atty. Docket: TOVEY=1A
In re Application of:	)	Conf. No.: 1869
Michael TOVEY	)	Art Unit: 1614
Appln. No.: 09/243,030	)	Examiner: R. Cook
Filed: February 3, 1999	)	Washington, D.C.
For: THERAPEUTIC APPLICATIONS OF HIGH DOSE INTERFERON	)	

DECLARATION

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, Mail Stop Amendments
401 Dulany Street
Alexandria, VA 22314

Sir:

I, the undersigned Michael Tovey, Ph.D., hereby declare and state as follows.

I am Director of the Laboratory of Viral Oncology CNRS UPR9045 at the Institut Andre Lwoff (French National Cancer Institute), INSERM (French National Institute of Health). I am also the named inventor on the present application. My *Curriculum Vitae* is attached hereto as Exhibit A.

I am aware of international patent publication no. WO 93/21229 of Amgen (hereinafter "Amgen"). The abstract of this publication reads:

> Methods for the treatment of cell proliferation disorders, viral infections, and other conditions without causing

> significant side effects normally associated with interferon therapy, involving administering to a patient in need thereof a therapeutically effective amount of consensus human leukocyte interferon are disclosed. Also disclosed are pharmaceutical compositions of consensus human leukocyte interferon.

I further note that one of the objects of the invention, specified at page 4, lines 16-22, reads as follows:

> Therefore, an object of this invention is the treatment of conditions that are susceptible of treatment with an interferon, wherein the undesirable side effects normally associated with alpha interferon treatment are significantly diminished compared to currently practiced treatment regimens or eliminated entirely.

The first sentence of the Summary of the Invention reads:

> The invention encompasses methods of treatment of various conditions susceptible of treatment with an interferon, involving administering to a mammal, preferably a human, a therapeutically effective amount of consensus human leukocyte interferon (IFN-con).

At page 5, lines 2-7, the Summary of the Invention states:

> The conditions that may be treated in accordance with the present invention are generally those that are susceptible to treatment by alpha interferons. In other words, IFN-con is useful to treat substantially the same conditions that may be treated with alpha interferons, such as Intron® A.

Accordingly, it is my understanding from a reading of this entire publication, and particularly the portions quoted above, that the invention disclosed therein relates only the substitution of IFN-con for other types IFN- in treatment regimens that are otherwise well known using IFN-. There is no disclosure in this publication of any new

conditions alleged to be treatable by IFN- nor any new modes of administration of IFN-. It merely refers to what was known in the art, at the time that the application was filed, with respect to indications and modes of administration.

With respect to modes of administration, the Amgen publication states at page 13, lines 23-30:

> The route of administration will preferably be by injection into the blood of a mammal where the injection may be intravenous, intramuscular, subcutaneous or intralesional. Administration may also be by oral or nasal routes. The suitability of a given pharmaceutical composition for a given route of administration will be apparent to one skilled in the art.

One of ordinary skill in art, as of the effective filing date of my above-identified application, i.e., the 1996-1997 timeframe, would not consider this reference to "oral or nasal routes" to encompass oromucosal administration.

The mechanism of action of oromucosal administration of interferons involves contact with specific high affinity receptors and activation of cellular components of the lymphoid tissue lining or surrounding the oromucosal cavity and does not involve absorption of biologically active interferon into the bloodstream, and my above-identified patent application so states.

In the 1996-1997 timeframe, one of ordinary skill in the art would have understood the term "administration by oral route," particularly as this terminology is used in the context of the Amgen publication, as meaning administration into the bloodstream via the gastrointestinal tract. In this

regard, reference is made to the list of references known in that timeframe relating to the administration of interferon by the oral route, and the abstracts thereof, attached hereto as Exhibit B. Those of ordinary skill in the art during this timeframe would not consider oromucosal administration of interferon to be encompassed by, or otherwise suggested by, a general reference to administration by the oral route.

Furthermore, during the 1996-1997 timeframe one of ordinary skill in the art, when encountering reference to administration of interferon by the nasal route, particularly as this terminology is used in the Amgen publication, would understand that such mode of administration involves absorption into the bloodstream via the respiratory tract after inhalation through the nose into the lung. In this regard, reference is made to the list of references known as of that timeframe relating to administration of interferon by the nasal route, and the abstracts thereof, attached hereto as Exhibit C. One of ordinary skill in the art during the 1996-1997 timeframe would not consider a general reference to administration of interferon via the nasal route as encompassing or otherwise suggesting oromucosal administration.

In my opinion, the present invention, involving the oromucosal administration of interferon, which does not involve absorption into the bloodstream, would not have been obvious from those references that were known in the 1996-1997 timeframe, such as the Amgen publication, that related to

administration of interferon by the oral or nasal routes; those of ordinary skill in the art would have understood that administration by the oral or nasal routes requires eventual absorption into the bloodstream.

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

24th May 2005
Date

Michael Tovey
Michael Tovey

Relevant Publications re Administration of Interferon by the Oral Route

1. Brod et al, "Ingested IFN-alpha has biological effects in humans with relapsing-remitting multiple sclerosis", Mult Scler 3(1):1-7 (1997 Feb)

2. Brod et al, "Oral administration of IFN-alpha is superior to subcutaneous administration of IFN-alpha in the suppression of chronic relapsing experimental autoimmune encephalomyelitis", J Autoimmun 9(1):11-20 (1996 Feb)

3. Vriesendorp et al, "Oral administration of type I interferon modulates the course of experimental allergic neuritis", Autoimmunity 24(3):157-165 (1996)

4. Brod et al, "Oral administration of human or murine interferon alpha suppresses relapses and modifies adoptive transfer in experimental autoimmune encephalomyelitis", J Neuroimmunol 58(1):61-69 (1995 Apr)

5. Brod et al, "Modification of acute experimental autoimmune encephalomyelitis in the Lewis rat by oral administration of type 1 interferons", J Interferon Cytokine Res 15 (2) : 115-122 (1995 Feb)

6. Brod et al, "Suppression of relapsing experimental autoimmune encephalomyelitis in the SJL/J mouse by oral administration of type I interferons", Neurology 44(6):1144-1148 (1994 Jun)

Relevant Publications re Administration of Interferon by the Nasal Route

1. Giosue et al, "Minimal dose of aerosolized interferon-in human subjects: biological consequences and side-effects", Eur Respir J 9:42-46 (1996 Jan)

2. Niven et al, "Systemic absorption and activity of recombinant consensus interferons after intratracheal instillation and aerosol administration", Pharm Res 12(12):1889-1895 (1995 Dec)

3. Halme et al, "Inhaled recombinant interferon gamma in patients with lung cancer: pharmacokinetics and effects on chemiluminescence responses of alveolar macrophages and peripheral blood neutrophils and monocytes", Int J Radiat Oncol Biol Phys 31(1):93-101 (1995 Jan)

4. Halme et al, "Pharmacokinetics and toxicity of inhaled human natural interferon+ in patients with lung cancer", Respiration 61(2):105-107 (1994)

5. Mitsutoshi T, "Method for the treatment of ATL and the inhalant for the same", EP 0 396 903, date of publication November 14, 1990